SUMMARY MINUTES

MEETING OF THE CIRCULATORY SYSTEM DEVICES ADVISORY PANEL

OPEN SESSION

May 29, 2003

Gaithersburg Holiday Inn
Gaithersburg, MD

Circulatory System Devices Advisory Panel Meeting

May 29, 2003

Attendees

Chairperson
Warren K. Laskey, M.D.
University of Maryland School of Medicine

Executive Secretary
Geretta Wood
Food and Drug Administration

Voting Members
Cynthia Tracy, M.D.
Georgetown University Hospital

Consultants
Francis R. Gilliam III, M.D.
Virginia Cardiovascular Specialists

William Maisel, M.D.
Brigham & Women's Hospital

David S. Schwartzman, M.D.
Presbyterian University Hospital Pittsburgh

Sharon-Lise Normand, Ph.D.
Harvard School of Public Health

Albert Waldo, M.D.
University Hospitals of Cleveland

Consumer Representative
Allen Hughes, Ph.D.
George Mason University

Industry Representative
Michael C. Morton
Sorin-COBE CV, Inc.

FDA Participants
Bram Zuckerman
Director
Division of Cardiovascular Devices

Cindy Demian, M.S.B.E.
Lead Reviewer

Lesley Ewing, M.D.
Clinical Reviewer

Heng Li, Ph.D., Statistical Reviewer

CALL TO ORDER

Panel Chair Warren K. Laskey, M.D., called the meeting to order at 9:16 a.m. **Executive Secretary Geretta Wood** read the conflict of interest statement. Full waivers had been granted to David S. Schwartzman, M.D., and Albert Waldo, M.D., for their interests in firms in matters that could be affected by the panel's recommendations. The Agency took into consideration other matters concerning Drs. Waldo and Schwartzman as well as Cynthia Tracy, M.D., and Francis R. Gilliam, III, M.D., for their interests in firms at issue but in matters not related to the day's agenda; they could participate fully in the panel's deliberations. In addition, Industry Representative Michael Morton reported interests in firms at issue. Dr. Laskey then asked the panel members to introduce themselves. Albert Waldo participated by conference call.

Ms. Wood read the appointment to temporary voting status, which stated that panel consultants Sharon-Lise Normand, Ph.D., and Drs. Gilliam, Maisel, Schwartzman, Waldo, and White had been appointed to temporary voting status for the duration of the meeting. Dr. Laskey was appointed as acting chair for the duration of meeting.

FDA PRESENTATION

Marian Kroen, Office of Surveillance and Biometrics, presented information on diathermy interactions with implanted leads and implanted systems with leads. FDA received adverse event reports on two patients with deep brain stimulators (DBS) who died following treatment with shortwave diathermy. FDA convened an expert panel to examine the problem; at the same time, Medtronic performed in vitro testing to assess the effect of diathermy on DBS systems and provided the results to FDA. The company found a temperature rise of 55ºC at the DBS lead electrode during 15-minute diathermy exposure and a temperature rise of 27ºC at a pulse rate of 8 and amplitude of 10 (the setting for the adverse events).

FDA's expert committee determined the need for more testing to determine the scope of the problem. FDA tested active implants and found that the temperature rise at the lead electrode is high whether or not a pacemaker is connected. The cardiac lead and pacemaker system showed the highest temperature rise (48.8ºC). The Spinal Cord Stimulator system and lead had the second highest temperature rise (27.6ºC). The temperature rise appears to be highest with shallowly implanted leads. FDA tested nonactive implants and found minimal heating (1º to 3.6ºC) for devices such as a 4-inch screw and a fracture plate.

FDA's conclusions are that diathermy interactions involving dangerously high temperatures are limited to (1) implantable systems with metallic (conductive) leads and (2) implanted metallic leads themselves. The theory is that the implanted lead acts like an antenna to receive energy; power is dissipated in the tissue where there is no insulation. The current density, and thus the temperature, at the lead electrodes can be very high, due to the small surface area of the electrodes. Both shortwave and microwave diathermy produce an electromagnetic field that can interact with implanted leads. Ultrasound diathermy would have a different mode of interaction with implants (i.e., mechanical rather than electromagnetic).

It is unclear why no injuries for interactions of diathermy with cardiac pacemakers and leads have been reported. Testing shows high lead electrode temperatures in pacemakers. FDA has received two reports of diathermy-related damage to pacemakers (but not to the heart). Possible reasons for the lack of reports may be inadequate warnings; in addition, blood flow in the heart carries away heat. Diathermy often takes place at some distance from the heart. It is possible that damage has occurred, but no one has connected it with diathermy. Also, the brain has no pain receptors, but the heart does, so patients report pain before significant diathermy-related injury occurs.

FDA has recommended changing the labeling on metallic leads and lead systems as well as on diathermy equipment. It issued a public health notification and published a journal article in *Patient Safety News.*

Panel members asked questions on the nature of the brain injuries associated with the deaths. They observed that researchers might not know if ablation took place at the tip of the pacemaker lead unless it was disruptive. Ms. Kroen noted that chronic pain institutes that use diathermy have been advocating that the technique not be used on people with pacemakers, but they had no evidence to back up their caution. Dr. Laskey noted that an observational study might be useful.

OPEN PUBLIC HEARING

No comments were made.

SPONSOR PRESENTATION

Marianne Baldwin, vice president, Regulatory, Clinical, and Quality, Cardima, introduced the sponsor presenters and provided background information on the company and the catheters it markets. She noted that a benefit of the Revelation series is that the catheters create continuous lesions. The Revelation Tx microcatheter is indicated for treatment of atrial fibrillation (AF) in patients with drug refractory paroxysmal AF by mapping, pacing, and ablating with a set of continuous linear lesions in the right atrium.

G. Neal Kay, M.D., professor of medicine, director of electrophysiology, University of Alabama–Birmingham, presented information on AF epidemiology and treatment options. AF can be classified as persistent, paroxysmal, and permanent. Permanent AF is refractory to

drugs and other treatment. Drug therapy has limitations. The pulmonary vein (PV) plays a role in AF initiation, but results of PV ablation are better for paroxysmal AF than for persistent AF. The risks of PV ablation are significant and include PV stenosis, stroke, tamponade, and major bleeding. No multicenter prospective trials of PV isolation have been performed. Surgery works by preventing PV triggers and interrupting macroreentry. Bi-atrial surgery generally produces better outcomes than left atrial surgery alone. Some study results demonstrate that the right atrial Maze operation may help prevent AF. Cardima has demonstrated this approach in a clinical study.

Hugh Calkins, professor of medicine, director of electrophysiology, Johns Hopkins Medical Center, an investigator in the Cardima clinical trial, stated that preclinical studies found the device to be biocompatible and reliable; it is compliant with ISO 10993 requirements as well as with mechanical and electrical performance requirements of the Massi guidelines. Animal studies demonstrated good results in terms of lesion formation and reduction of AF. Compared with lesions created with a standard device, lesions produced with the Revelation catheters are narrower, deeper, more continuous, more linear, and more likely to be anchored to an anatomic structure. The differences in lesions may facilitate AF cure with a catheter-based Maze procedure.

Dr. Calkins then described the protocol development and design of Cardima's clinical study. The rationale for the right atrial (RA) procedure is that the optimal lesion set for AF treatment is unknown; safety and efficacy of PV isolation are unknown and risks are high; and RA ablation is likely to be less risky than left atrial ablation. The approach may thus be more widely applicable. After presenting background on the development of the study protocol, Dr. Calkins noted that the study had incorporated all of the Panel's earlier recommendations.

Dr. Kay listed the study inclusion and exclusion criteria; study objectives were reduction in symptomatic AF episodes, safety, and improvement in quality of life. During the surgery, lesions were made in the postlateral, anterior, and septal walls of the RA as well as in the isthmus. Follow-up office visits took place at 1, 3, 6, and 12 months postoperatively, and a telephone interview took place at 24 months. In addition, patients provided weekly and symptomatic transmissions using a cardiac event monitor at baseline and months 1, 3, and 6. Primary clinical endpoints were frequency of spontaneous symptomatic AF episodes and incidence of adverse events. The secondary clinical endpoint was quality of life based on SF-36 and Atrial Fibrillation Severity Score (AFSS) data.

Acute procedural success was defined as reduction in amplitude, fragmentation, or widening of local electrograms; appearance of split potential; and increase in pacing threshold. The primary endpoint was ?? 50 percent reduction in AF episodes for patients with?? 5 AF episodes per month and ?? 75 percent reduction in AF episodes for patients with ?? 3–4 AF episodes per month. Clinical success was defined as reduction in AF episodes while maintaining the same antiarrhythmic drug (AAD) regimen or a reduced dosage. The study yielded 80 evaluable subjects at 6-month follow-up. The sample size was based on the estimated patient success rate and was specified in the FDA-approved protocol.

Abraham G. Kocheril, head of cardiac electrophysiology, Carle Heart Center, principal investigator of the Cardima study, presented the study results, including data on patient demographics and attrition. Twenty sites participated. Of the patients enrolled in the study, 89 were male, and 84 had cardiovascular disease. At baseline, 32 patients experienced 3–4 symptomatic AF episodes per month, 45 experienced 5–9 episodes, and 39 experienced 10 or more episodes. Mean SF-36 scores at baseline were significantly below average in several areas.

A total of 110 of 118 patients (93 percent) met the criteria for acute procedural success (APS). Dr. Kocheril noted that APS was used as a surrogate for clinical effectiveness because initial plans to record specific measurements of APS became unwieldy. At 6 months, 69 of 81 patients (85 percent) met the primary endpoint; 54 percent experienced no symptomatic AF episodes at 6 months. People with the highest number of symptoms benefited the most. The reduction in common arrhythmia symptoms was significant. With regard to the secondary endpoint, significant improvement was seen in SF-36 and AFSS scores.

Four of 123 patients met FDA's definition of experiencing major complications. No reports of mortality, cardiac perforation, arterial injury, stroke, or thromboembolism were received; 73 percent of participants reported no adverse events.

Dr. Kocheril clarified that the Revelation device was used for all nonisthmus linear lesions; it could ablate some, but not all, subeustacian isthmus lines. Investigators therefore used clinically available 4 mm ablation catheters to create the flutter line. The NavAblator catheter was developed for Phase III of the study, but some investigators preferred to use their standard 4 mm catheters. The fact that investigators used non-Revelation catheters to create the flutter line did not materially affect the results of study. Although the protocol stated that "subjects electing to receive implantable pacemakers prior to 6 month follow-up will be considered failures," the intent was that subjects should not require adjunctive pacemaker therapy to address AF. Most study subjects receiving pacemakers did not receive them to treat AF. Moreover, patients with pacemakers were not excluded from the study. Three patients received pacemakers within 10 days of the procedure. All three had known preexisting sinus node dysfunction.

As determined by clinical site, 19 of the 69 successful patients had an increase in their AAD regimen; thus the clinical success rate was 50/81 (62 percent). Given the current

information on the efficacy of AADs, it is difficult to determine the true increase in an AAD regimen. Nineteen of 69 successful patients had an increase in their AAD regimen; 10 were "increased" to an AAD regimen to which they were previously refractory. Even for those patients, the marked reduction in AF episodes is likely a result of the ablation procedure.

The study experienced difficulty with transtelephonic event monitoring (TTM) compliance. However, no significant differences were found in the AFSS mean scores by TTM transmissions. TTM data indicate improvement in AF.

Dr. Kay summarized the sponsor's presentation. RA linear ablation offers a reasonable level of success for control of paroxysmal AF. Most patients continued to require AADs, although at the same or lower dose. Success was accomplished with a low risk of serious complications. The lower risks of the procedure allow it to be performed by a wider range of physicians than the complex LA ablation procedure. It may become a first-line therapy for patients who have failed drug therapy. Results provide reasonable assurance of safety and efficacy.

Panel Questions for Sponsor

Panel members asked for clarification on issues related to the patients' coumadin use before and after ablation; on the general difficulty of creating linear lesions with the multiple-electrode catheters and how operators knew they had an adequate lesion; on the rationale for the choice of lesion sites; on the impact of rate control on patient outcomes; on TTM compliance; on whether reduction of symptoms related to AF could be due to rate control, social factors, or anesthetation; and on how the sponsor defined increases or decreases in medication regimens. Sponsor representatives provided the additional information.

FDA PRESENTATION

Cindy Demian, M.S.B.E., lead FDA reviewer, listed the members of the review team and reviewed the device's indications for use, noting that the sponsor was using a shorter version than initially proposed. She summarized the history of FDA's interactions with Cardima and emphasized that FDA had consistently told Cardima that the use of noninvestigational catheters would be considered failures. In May 2001, FDA informed Cardima of its concerns about patient noncompliance with TTM and the varying definitions of acute success. The Revelation Tx microcatheter met the preclinical goals of safety and reliability; however, several device and cable failures occurred in the clinical trial that were not predicted in device testing.

Lesley Ewing, M.D., clinical reviewer, reviewed the proposed indications for use that were to be used with the clinical trial and noted that they differed slightly from the indications in the PMA. She summarized the study design and inclusion and exclusion criteria. FDA's information indicates that during the 30-day baseline preablation procedure, during which patients were screened to assess their eligibility for ablation, patients were aware that a minimum number of AF episodes were required, creating the possibility of bias.

The ablation procedure specified three linear lesions; the anterior lesion was optional. All lesions were to be attempted first with the Revelation catheter. If the tricuspid lesion was not successful, the NavAblator could be used. AF episodes were to be counted by TTM, and weekly TTM was compulsory during the 1-, 3-, and 6-month follow up, even without symptoms. After reviewing the definitions of the primary and secondary effectiveness endpoints and the definition of procedural success used in the trial, Dr. Ewing noted that the Agency thinks it is important to standardize medication use; this was not done in the trial, however.

The FDA review is based on different numbers from those used in the sponsor's report. An appendix to the FDA clinical review contains the data upon which the review team based its conclusions. The study data have many problems. The percentage of TTM reports that were diagnosed as AF ranged from 12.9 percent to 100 percent. It is unknown whether each transmission represents a discrete AF episode. Also, during the ablation procedure, not all patients had the same lesion set performed. The Revelation Tx catheter was used for all septal and lateral linear lesions, but some patients had only a noninvestigational catheter used for the tricuspid isthmus lesion. The noninvestigational catheters were from five different manufacturers and included a cooled tip catheter. In addition, successful bidirectional conduction block was measured in 71 percent of patients; in comparison, noninvestigational catheters used alone at the tricuspid isthmus were 100 percent successful. It was not clear how the investigators defined a successful lesion, and the study had poor compliance with TTM. Dr. Ewing observed that the sponsor had acknowledged that "sufficient data to demonstrate either success or failure for the procedural endpoint are not available."

FDA calculated that 42 of 88 evaluable patients reached the primary effectiveness endpoint. Of the 43 patients who reported or transmitted no events, 11 had some kind of treatment for AF subsequent to the ablation, including surgical Maze, new or increased amiodarone use, and AV node ablation. A total of 26 of 82 patients had an increase in AAD regimen. Ten of 88 had AV node ablation, and 2 of 88 had surgical Maze. The data on secondary outcome are equivocal. Several events should have been included in the sponsor's count of major complications; 5 of 116 patients, or 4.3 percent, had one or more major complications. Of possible safety concern is that 20 patients had a pacemaker implanted 1 day to 1.5 years after

ablation; 9 of them also had AV node ablation. In addition, 8 percent had pacemakers implanted within 6 months of the ablation procedure without AV node ablation.

Heng Li, Ph.D., statistical reviewer, presented the statistical summary. The study was a single-arm, nonrandomized, multicenter trial with subjects serving as their own controls. The protocol did not include a proposed rule that specified what the results had to be in order for the investigational device to be approved. Dr. Li made general comments concerning the methodological problems of single-arm pretest–posttest studies.

A major problem with the Cardia study is that noninvestigational devices were used on patients who were not randomly selected. The patients who were treated only with investigational devices did not form a random subgroup of all the study subjects. The missing piece of the puzzle consists of the outcomes that would have been observed for patients treated with noninvestigational devices if they had been treated with investigational devices only.

Dr. Ewing summarized FDA's concerns. The ablation procedure was not the same for all patients in the study. As a result of the study design, there could be bias toward reporting AF episodes at baseline and against reporting in the 6th month. APS cannot be assessed for the procedures in the study due to incomplete reporting of the various acute procedural endpoints. Some patients had further procedures to treat paroxysmal AF after the ablation procedure, and 20 patients had had a pacemaker implanted by 1.5 years postprocedure. There was poor compliance with TTM during the 6th month. The quality of life data include patients with an ambiguous number of baseline episodes and some patients who had an AV node ablation procedure. From the clinical and statistical perspective, it is not clear if the data can support any conclusion about the safety and effectiveness of the investigational device system.

OPEN COMMITTEE DISCUSSION

Francis R. Gilliam III, M.D. , panel reviewer, noted that the time required for the procedure seemed excessive. Sponsor representatives attributed the lengthy procedures to the mapping requirements and the time required to create the flutter line lesion. Dr. Gilliam also raised concerns over the TTM data and the possibility of placebo effect. He pointed out that five patients had pacemakers prior to entering the study and suggested that pacemaker counters could have been used to evaluate AF episodes. In addition, some patients may have reported a single AF episode as multiple episodes. He asked for clarification from the sponsor as to why 20 centers could enroll only a relatively small number of patients; Dr. Calkins noted that many patients found the protocol cumbersome and opted for off-label use, and some centers steered patients toward other procedures, such as PV isolation. Dr Gilliam also asked for information as to why the NavAblator was more useful than a regular ablation catheter. Dr. Calkins replied that the catheter is "incredibly flexible and floppy and conforms well to a beating heart"; in addition, it produces better lesions.

William Maisel, M.D., panel reviewer, raised concerns about the study's methodology, including the procedural endpoints; use of multiple catheters; and assessment of pre- and postprocedure AF. An optimal lesion set was not identified, and study endpoints were not consistently measured or recorded on data forms. As a result, it would be difficult to inform physicians about how they were to know when the procedure is completed. Dr. Kocheril said that if the study were being done today, electromapping techniques would be used.

Dr. Maisel noted that the use of multiple and off-protocol catheters makes it challenging to interpret the data. In addition, the issue of postprocedure pacemaker implantation is important; the rate in the study seems high.

Finally, the pre- and postprocedure AF assessment process has several potential sources of bias. Patients were aware that a certain number of AF episodes were required to get into the study. More significant is that nearly two-thirds of the patients did not provide the minimum number of required TTM transmissions. Patients without follow-up data should have been classified as missing. In response to a question from Dr. Maisel, Dr. Ewing noted that if a patient said he or she had no episodes in a month but did not have transmission data, the information was included in the FDA analysis. Dr. Maisel noted the likelihood of recall bias and was troubled by the inadequate follow-up data. Patients withdrawn early from the study should be classified as failures. Only 48 percent reached the efficacy endpoint, and only 27 percent of those had clinical success as defined in the protocol.

Dr. Waldo concurred with the other panel reviewers about the lack of rigor in picking the data. The TTM data are especially worrisome: The crux of the study is to decrease the burden from AF, but the evidence is missing. Just because patients do not report AF does not mean that one can assume that nothing is happening; too many participants got pacemakers and AV node ablations. Dr. Kay noted that the goal of treatment was improvement of AF symptoms as reported by patients. When patients feel well, they do not take time to transmit the data. Dr. Waldo replied that he understood what the sponsor was saying, but objectively, the data are not there. Dr. Kay noted that the TTM compliance was as good as could be expected; the company did what it was asked to do. The procedure is safe, and whether efficacy is 80 percent or 40 percent, it is still an improvement. Dr. Waldo remained unconvinced.

Panel members echoed the reviewers' comments concerning the deviations from the study protocol: A sizeable number of patients had noninvestigational devices, and no protocol for AAD use was specified. Panel members also concurred with the reviewers' concerns about

which patients should have been included in the data analyses and asked for clarification as to the differences between the FDA's and the sponsor's analyses. Dr. Ewing replied that FDA included patients who went on to have another procedure if linear ablation failed; the sponsor categorized those patients as withdrawn. Also, the sponsor counted patients who received pacemakers as successes; according to the protocol, they were to be called failures. FDA counted seven patients as having an increase in drug regimen that the sponsor did not.

Panel members expressed concern over the sample size, definition of endpoints, and TTM follow-up. Panel members also noted that the sponsor's claim of continuous linear lesions is unproven; it is likely that very few lesions were continuous. Electrophysiologic efficacy is unclear: Experience shows that few patients remain without another procedure after RA ablation. In addition, thermometry is not a good monitoring technique for extended use. The sponsor did not adjust for the fact that multiple sites participated or stratify the data by the number of episodes at baseline. In addition, the procedure time seemed unduly long; in several cases, patients experienced skin burns.

A substantial minority of patients seem to have experienced burden reduction. However, the ability of patients to determine whether they were in AF seemed to decrease, which could have been due to nerve damage or the placebo effect.

Ms. Baldwin noted that the original protocol specified that the investigator could use the standard institutional procedure to create only the isthmus line. In the initial development of this protocol, it was discussed whether a flutter line was necessary, and it was concluded that it would not be fair to the patient to do ablation and not do the flutter line. FDA representatives replied that the agency had instructed the company that use of noninvestigational catheters in the trial would be considered failure. Dr. Tracy observed that the efficacy rate varied widely,

depending on who was analyzing the data: It would be "20-something percent strictly by protocol, 40 something allowing for nonprotocol catheters, and 80 percent going by the company's definition."

PANEL QUESTIONS

1(a) Please discuss how the multiple catheter combinations affect the conclusions that may be drawn from this study.

The panel concurred that the use of multiple catheter combinations precludes drawing conclusions from the data.

1(b) Please discuss the ability to analyze the device outcomes versus treatment outcomes in this study. In particular, can you comment on whether the safety and effectiveness results for this study may be attributable to one specific catheter? Do the treatment strategies employed in the study support the proposed indications for use statement?

The panel concurred that no conclusions could be drawn from the data.

2(a) Please discuss how the lack of a measurable procedural endpoint affects data analysis for this clinical trial.

The panel felt that it had covered the topic in its earlier discussion.

2(b) Please discuss whether the study provides sufficient information to instruct the user of the catheter system as to procedural goals or endpoints when treating an individual patient.

The panel concurred that the study does not provide sufficient information in this area.

3(a) Given that the patients knew that a certain amount of episodes were required to be admitted into the study, please discuss the potential problems with accuracy in the counting of episodes at baseline and at follow up.

Although the panel felt that the sponsor answered this question credibly, the event to be measured has great variability, and the sponsor's methods did not ensure accuracy. Dr. Waldo noted that most studies similar to this one ask patients to call back when normal rhythm is established. Better ascertainment needs to be ensured for both baseline and follow-up.

3(b) Please discuss how incomplete compliance with transmissions of rhythm strips impacts measurement of the primary effectiveness endpoint.

The panel concurred that incomplete compliance precludes interpretation of the data.

4. Please comment on whether the results of the clinical study provide reasonable assurance of safety for the intended use.

The panel concurred that safety was not an issue, but the device's efficacy is questionable.

5. Given the lack of a control group, please comment on how one would determine an acceptable rate of permanent pacemaker implantation.

Panel members noted that the rate of pacemaker implantation did not seem out of line with existing data on Maze procedures. The findings reflect some of the study's lack of rigor. It would have been better to deal with sinus node dysfunction at the outset. This patient population has a fairly high incidence of sinus node dysfunction, and many drugs for treating AF add to the problem.

6(a) Do the clinical data provide a reasonable assurance of effectiveness of the system?

The panel concurred that the data do not demonstrate effectiveness of the system.

6(b) Does a significant decrease in paroxysmal atrial fibrillation episodes constitute adequate evidence for effectiveness?

The panel concurred that decrease in paroxysmal atrial fibrillation episodes is an adequate endpoint; however, it is unclear that a decrease actually occurred.

7. A secondary effectiveness endpoint of the study was improvement in quality of life. Given the potential bias introduced with a non-randomized unblinded study, please comment on the device system's demonstration of improvement in quality of life.

The panel noted that the data are subjective, so it cannot be determined why patients felt better. The survey instruments were developed in randomized trials, not this kind of study, and placebo effects are a possibility.

8(a) If you believe that additional data are necessary to demonstrate reasonable assurance of safety and effectiveness of the Cardima ablation system, please address the following questions. Please clarify if additional analyses on the current data set may be performed to provide adequate information to support safety and effectiveness.

The panel concurred that the current data set is not likely salvageable.

8b. Please comment if the collection of additional data using the current patient selection criteria and outcome measures would be adequate to support safety and effectiveness.

The panel suggested approaches such as obtaining better 6-month follow-up data on remaining patients or more detailed post hoc EEG analysis, such as comparing data from a month of monitoring with data obtained at baseline. However, the panel concurred that the fundamental problem is the deviation from the protocol throughout the study.

8(c) Please comment if a new prospective trial is needed to provide adequate information to support safety and effectiveness.

The panel agreed that a new prospective trial is most likely necessary. With the current data set, it is difficult to rule out regression to the mean and the placebo effect. Dr. Zuckerman asked the panel if it thought a percentage reduction in symptomatic AF compared with baseline AF was an acceptable or clinically useful measure. The panel concurred that it was an adequate measure; however, to demonstrate efficacy of an invasive procedure, it is important to document something beyond a placebo effect. An objective outside measure beyond the patient, such as repeat hospitalization, is needed.

9(a) Does the Indications for Use . . . adequately define the patient population and procedural use for which the device will be marketed?

The panel concurred that the patient population and procedural use seem well defined.

9(b) Based on the study results, please discuss whether the proposed warnings, precautions, and contraindications are acceptable.

The panel concurred that the language needs to be modified as discussed in its deliberations. Dr. Gilliam reiterated his concern that no clear endpoints are specified for the procedure.

9(c) Please discuss whether the instructions for use adequately describe how the device should be used.

The panel agreed that the instructions adequately describe how to use the device.

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No comments were made.

VOTE

Ms. Wood read the voting options. The panel voted unanimously to not recommend approval.

When asked to state the reasons for their votes, panel members stated that the sponsor had not provided reasonable assurance that device is effective. The device may have a role in the clinician's armamentarium, but the data are too ambiguous. The clinical study lacked rigor: The assessment of endpoints was inconsistent, and the data analysis was flawed.

ADJOURNMENT

Dr. Laskey thanked the participants and adjourned the meeting at 4:48 p.m.

I certify that I attended this meeting of the Circulatory System Devices Advisory Panel Meeting on May 29, 2003, and that these minutes accurately reflect what transpired.

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Geretta Wood
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

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Warren K. Laskey, M.D.
Chairperson

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